PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H. Director, State Department of Public Health

Chloramphenicol—Another Warning

CHLORAMPHENICOL has been a popular broad-spectrum antibiotic since its introduction in 1948, because of its effectiveness and the absence of annoying side effects. Since 1952, however, prominent warnings about serious and often fatal blood dyscrasias have been part of the approved labeling of the drug and this information has been widely disseminated in the medical and lay press.

A 1964 study showed that out of a random sample of 138 deaths in California attributed to aplastic anemia between 1 January 1957 and 30 June 1961, a total of 30 patients (22 percent) had had therapy with chloramphenicol.[1]

In 1963 two California State Senate resolutions expressed concern about hazards associated with chloramphenicol therapy and asked the California State Department of Public Health and the California Medical Association to investigate further the risk associated with administration of chloramphenicol.[2,3]

In response to that request, a study was planned and conducted jointly by the Committee on Adverse Drug Reactions of the California Medical Association and the staff of the California State Department of Public Health, with the cooperation of the California Pharmaceutical Association. It was reported to the legislature 1 January 1967 and published in the *Journal of the American Medical Association.*[4]

The study involved a search of death certificates to discover every fatality in California due to aplastic anemia during an 18-month period between 1 January 1963 and 30 June 1964. Out of a total of 409 death certificates referring to hematologic disorders of possible significance, 290 were scrutinized. The cases were assigned to physician-consultants having experience in hematology who reviewed all available material to determine whether or not the diagnosis of aplastic anemia could be made, regardless of cause of death on the death certificate, and whether chloramphenicol or any other identifiable agent was involved.

Among the 290 deaths reviewed, 60 cases of aplastic anemia were found. In ten cases, chloramphenicol had been administered at some time before the onset of anemia. Fatal aplastic anemia developed after a single course of chloramphenicol in five patients, on second exposure several years after the first course in three, and on third exposure in two. Dosage was not unusually large or prolonged in any of the ten patients. Among the 50 patients not exposed to chloramphenicol seven had been exposed to other potentially toxic agents.

The risk of fatal aplastic anemia in association with chloramphenicol was calculated as 13 times that without exposure to the drug. The study team concluded that to assume a probable risk 13 times the normal risk appears totally unwarranted in the treatment of minor conditions or for prophylactic therapy or for treating infections, if a safer alternate drug is available. No reliable way exists to predict in which patients aplastic anemia may develop after chloramphenicol therapy.

A 1969 California State Assembly Resolution relative to the dangers of antibiotic drugs asks that the State Department of Public Health continue its investigation of fatal aplastic anemia and of deaths thought to be due to the use of chloramphenicol, and to send to the Assembly early in 1972 a report of its findings and its recommendations as to needed legislation.[5]

The joint study by the Committee on Adverse Drug Reactions of the California Medical Association and staff of the California State Department of Public Health refined previously available quantitative data concerning the occurrence of fatal aplastic anemia in the California population, and the risk of serious adverse reactions associated with the use of chloramphenicol.

The study also pointed up the value and the need for further cooperative effort by responsible agencies to establish more effective procedures for the evaluation of quantitative factors relating to the occurrence of adverse drug reactions. As pointed out by Weston,[6] the usual side effects of drugs are reasonably adequately handled from a *qualitative* viewpoint in responsible sources of drug information. However, *quantitative* information, with accurate numerators and denominators or

accurate comparative incidence ratios, leaves much to be desired. Broad programs for the collection of data on adverse drug reactions in recent years have for the most part not provided significant numerator or denominator data bearing on the ratio of risk to benefit. Nor have they delineated the comparative risk-to-benefit ratios of drugs used for similar disease entities. To provide information of this type, more extensive and intensive methods of screening cases and collecting drug usage data need to be developed.

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